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Novel perspectives on Amentoflavone's influence on cell cycle and apoptosis: exploring theoretical modulation of serine/threonine-kinases

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Abstract

Docking results suggest that Amentoflavone has a higher affinity for investigated serine/threonine-protein kinases, indicating potential interactions that may influence the activities of these kinases. The negative values of the binding energies signify strong and stable interactions, suggesting that Amentoflavone could be a key molecule in modulating the functions of these kinases, which play crucial roles in cellular processes such as cell cycle regulation and apoptosis.

Keywords: *Serine/threonine protein kinase, Amentoflavone, Molecular docking, Apoptosis*

1. Introduction

In enzymology, the term "serine/threonine protein kinase" refers to a category of enzymes within the transferase family. These enzymes are responsible for transferring phosphates to the oxygen atom of either a serine or threonine side chain in proteins, a biochemical process known as phosphorylation. Protein phosphorylation holds substantial importance in numerous cellular processes and serves as a crucial posttranslational modification (Cross *et al.*, 2000; Dudek *et al.*, 1997).

Serine/threonine kinases play pivotal roles in various cellular processes, contributing to the regulation of fundamental biological functions (Cross *et al.*, 2000; Dudek *et al.*, 1997). Here's an overview of their involvement:

1.1. Cell proliferation

Serine/threonine kinases are key regulators of cell cycle progression, controlling the transitions between different phases of the cell cycle. They influence processes such as DNA replication and cell division, thereby impacting cell proliferation (Mumby and Walter, 1993).

1.1.1. Programmed cell death (apoptosis)

These kinases are involved in the intricate signaling pathways that govern apoptosis, a highly regulated and essential process for the removal of damaged or unnecessary cells. Serine/threonine kinases can either promote or inhibit apoptosis, depending on the context and specific signaling pathways involved (Cross *et al.*, 2000).

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1.2. Cell differentiation

Serine/threonine kinases contribute to the regulation of cell differentiation, the process by which cells become specialized and acquire distinct functions. They influence signaling pathways that guide cells towards specific fates, determining their roles in tissues and organs (Ten Dijke *et al.*, 1994; Wang *et al.*, 2001).

1.3. Embryonic development

During embryonic development, serine/threonine kinases play crucial roles in orchestrating the intricate processes of cell division, differentiation, and tissue morphogenesis. They contribute to the formation and patterning of tissues and organs (Su *et al.*, 1996).

1.4. Signal transduction pathways

Serine/threonine kinases are integral components of various signaling pathways that relay information from the cell surface to the nucleus. These pathways are critical for cells to respond to extracellular signals and adapt to changes in their environment (McCubrey *et al.*, 2000; Posada and Cooper, 1992).

Examples of serine/threonine kinases include members of the cyclin-dependent kinase (CDK) family, mitogen-activated protein kinase (MAPK) family, and protein kinase B (Akt), among others (Dudek *et al.*, 1997; Graves *et al.*, 1995).

This brief theoretical study seeks to explore the potential role of Amentoflavone, a natural substance through an in silico approach employing Molecular Docking (Agarwal and Mehrotra, 2016), by Mcule Database (Odhar *et al.*, 2019).

General speaking, Amentoflavone, categorized as a biflavonoid, belongs to the flavonoid class characterized by the coupling of two apigenin molecules. Specifically, Amentoflavone features the coupling of these apigenin units at the 8 and 32 positions, resulting in the formation of a structure termed 32, 83-biapigenin. This compound is present in various plants, including Ginkgo biloba. Flavonoids, such as biflavonoids like Amentoflavone, are renowned for their potential health benefits and antioxidant properties. Ginkgo biloba, a plant with a history in traditional herbal medicine, contains Amentoflavone as one of its phytochemical constituents, contributing to the overall bioactivity of the plant (Xiong *et al.*, 2021; Yu *et al.*, 2017).

2. Material and methods

Serine/threonine kinases are performed in this work:

- RAC-beta serine/threonine-protein kinase (PDB Code 1o6l): Binding site center x(43,3729), y(31,1037), z(110,8303)
- Proto-oncogene serine/threonine-protein kinase pim-1 (PDB Code 3a99): Binding site center x(-9,2743), y(82,9438), z(-1,9399)
- Serine/threonine-protein kinase PLK1 (PDB Code 3fvh): Binding site center x(-0,3186), y(14,7623), z(8,7984)
- Serine/threonine-protein kinase Nek2 (PDB Code 2w5a): Binding site center x(-26,193), y(11,1522), z(16,5468)
- Serine/threonine-protein kinase 6 (PDB Code 1mq4): Binding site center x(-7,0463), y(27,7528), z(80,2108)
- Serine/threonine-protein kinase Chk1 (PDB Code 3ot3): Binding site center x(15,6907), y(-3,3932), z(11,8561)

3. Results and discussion

Serine/threonine-protein kinases are a class of enzymes within the transferase family. They play crucial roles in cellular processes, including the regulation of cell cycle progression, programmed cell death (apoptosis), cell differentiation, and embryonic development. These kinases catalyze the transfer of phosphate groups to serine or threonine residues in proteins, a process known as phosphorylation. This posttranslational modification influences protein activity and function, contributing to the intricate signaling pathways that govern various biological functions. Examples of serine/threonine-protein kinases include cyclin-dependent kinases, mitogen-activated protein kinases, and protein kinase B (Akt). Understanding their functions is essential for unraveling the complexities of cell biology and has implications for therapeutic development in

diseases associated with dysregulated cellular processes (Cross *et al.*, 2000; Dudek *et al.*, 1997; Mumby and Walter, 1993; Ten Dijke *et al.*, 1994; Wang *et al.*, 2001; Su *et al.*, 1996; McCubrey *et al.*, 2000; Posada and Cooper, 1992).

This study specifically delves into the potential interaction of Amentoflavone with Serine/threonine-protein kinases using Molecular Docking (Agarwal and Mehrotra, 2016) via the Mcule Database (Odhar *et al.*, 2019).

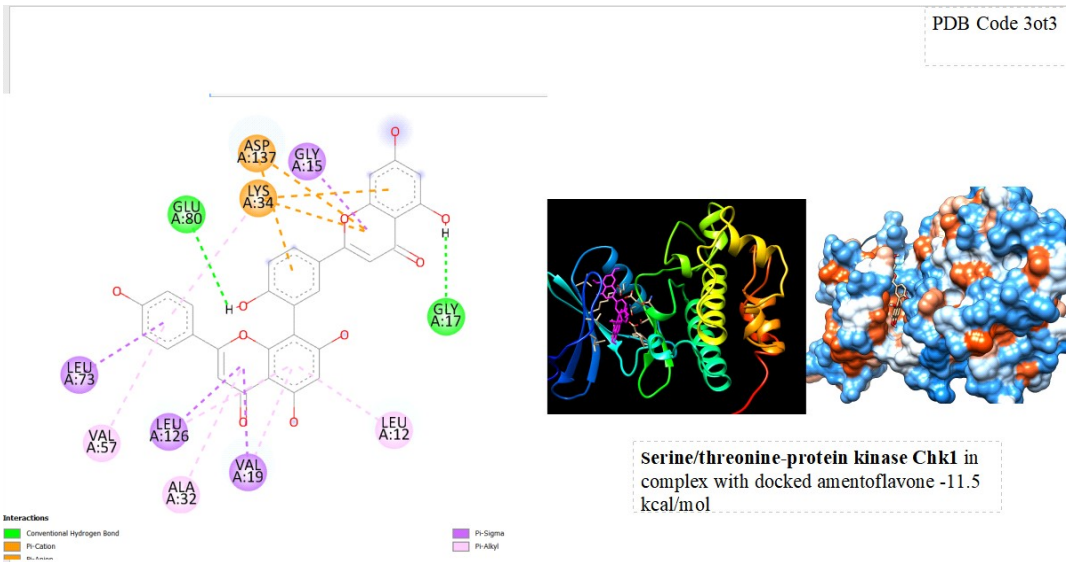

Figure 1: Displays the docking outcomes of Serine/threonine-protein kinase Chk1 in conjunction with Amentoflavone within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Amentoflavone

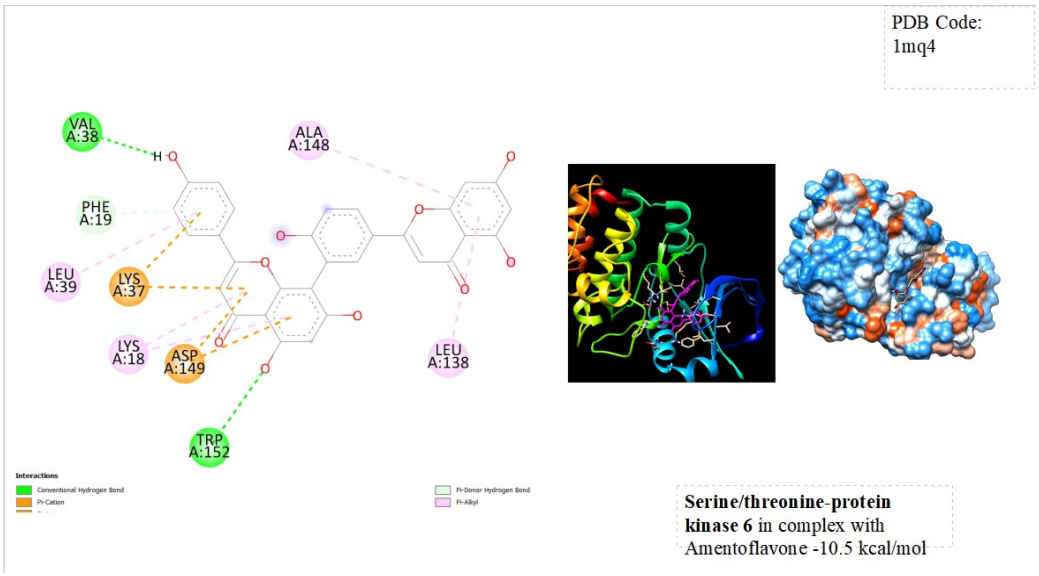

Figure 2: Displays the docking outcomes of Serine/threonine-protein kinase 6 in conjunction with Amentoflavone within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Amentoflavone

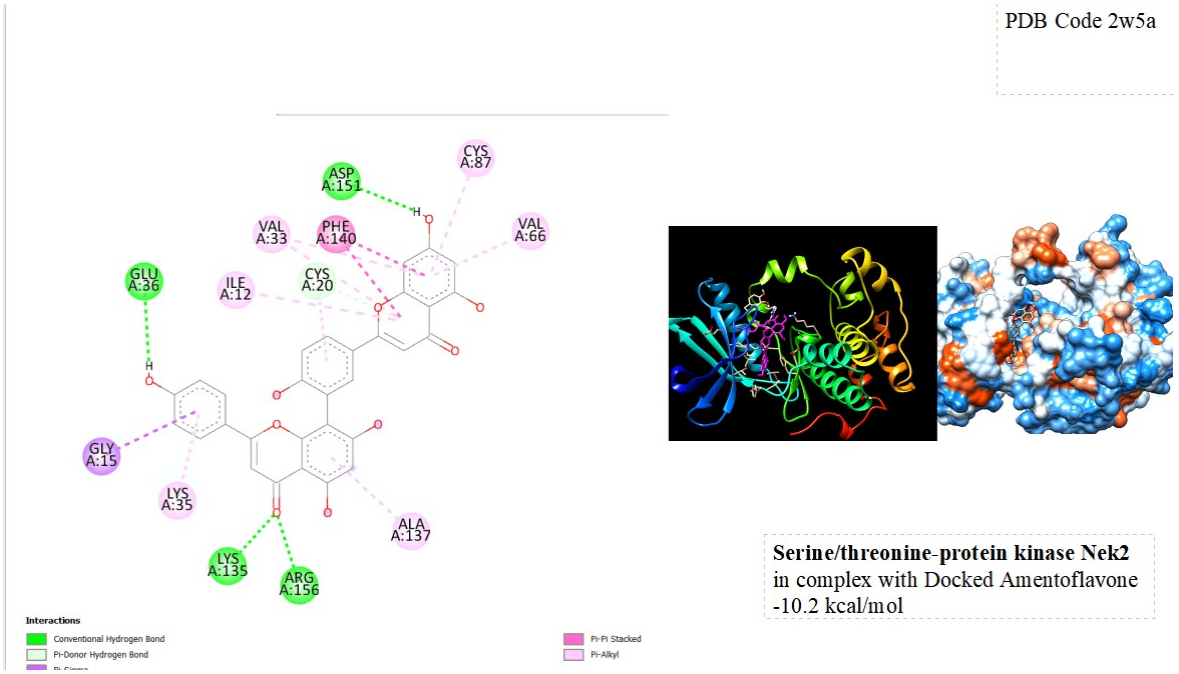

Figure 3: Displays the docking outcomes of Serine/threonine-protein kinase Nek2 in conjunction with Amentoflavone within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Amentoflavone

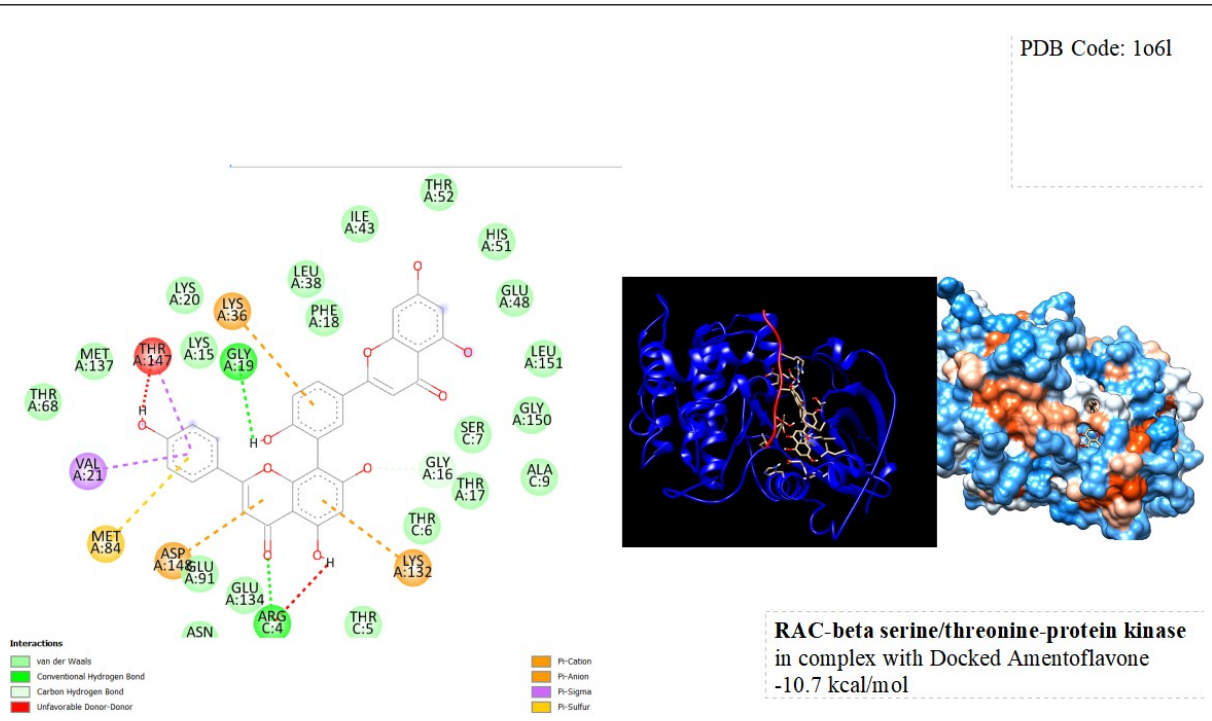

Figure 4: Displays the docking outcomes of RAC-Beta Serine/threonine-protein kinase in conjunction with Amentoflavone within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Amentoflavone

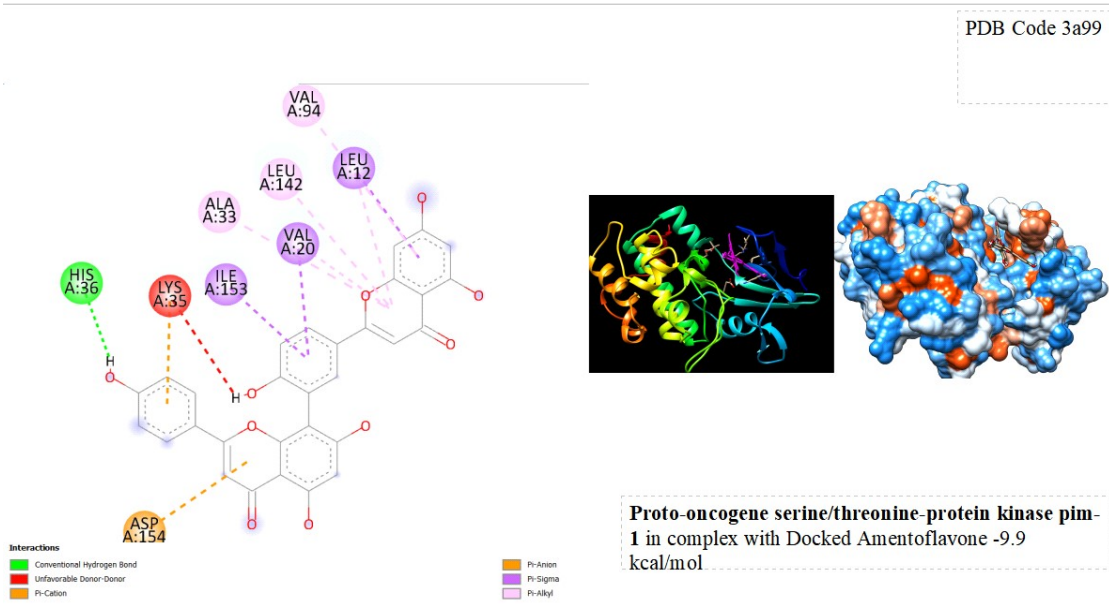

Figure 5: Displays the docking outcomes of Proto-oncogene Serine/threonine-protein kinase pim-1 in conjunction with Amentoflavone within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Amentoflavone

By employing Molecular Docking to compare binding energies across various serine/threonine-protein kinases, Amentoflavone emerges as a potentially key molecule influencing several biological processes. Table 1 illustrates the binding energy scores (kcal/mol) of Amentoflavone with the investigated serine/threonine-protein kinases. These scores provide valuable insights into the strength and specificity of the interactions, shedding light on the potential significance of Amentoflavone in modulating the activities of these kinases and, consequently, various cellular processes.

Table 1: Comparison of histone deacetylases with curcumin evaluated by mcule database with autodock vina

Serine/threonine-protein kinases	Binding energies (kcal/mol)
RAC-beta serine/threonine-protein kinase	-10.7
Serine/threonine-protein kinase Chk1	-11.5
Serine/threonine-protein kinase 6	-10.5
Serine/threonine-protein kinase Nek2	-10.2
Proto-oncogene serine/threonine-protein kinase pim-1	-9.9
Serine/threonine-protein kinase PLK1	-8.4

4. Conclusion

These results indicate that Amentoflavone demonstrates a higher affinity for the investigated Serine/threonine-protein kinases. The more negative the binding energy, the stronger and more stable the interaction. Therefore, the higher affinity suggests that Amentoflavone may have a notable influence on these kinases, indicating its potential significance in modulating cellular processes associated with these proteins.

Conflict of interest

Authors declare that they do not have any conflict of interest

Authors' contributions

Protocol designed by IVF. All authors read and approved the final manuscript.

References

Agarwal, S. and Mehrotra, R.J.J.C. (2016). An overview of molecular docking. *JSM chem*, 4(2): 1024-1028.

Cross, T.G., Scheel-Toellner, D., Henriquez, N.V., Deacon, E., Salmon, M. and Lord, J.M. (2000). Serine/threonine protein kinases and apoptosis. *Experimental cell research*, 256(1): 34-41.

Dudek, H., Datta, S.R., Franke, T.F., Birnbaum, M.J., Yao, R., Cooper, G.M., ... and Greenberg, M.E. (1997). Regulation of neuronal survival by the serine-threonine protein kinase Akt. *Science*, 275(5300): 661-665.

Graves, J.D., Campbell, J.S. and Krebs, E.G. (1995). Protein serine/threonine kinases of the MAPK cascade. *Annals of the New York academy of sciences*, 766(1): 320-343.

McCubrey, J.A., May, W.S., Duronio, V. and Mufson, A. (2000). Serine/threonine phosphorylation in cytokine signal transduction. *Leukemia*, 14(1): 9-21.

Mumby, M.C. and Walter, G. (1993). Protein serine/threonine phosphatases: structure, regulation, and functions in cell growth. *Physiological reviews*, 73(4): 673-699.

Odhar, H.A., Rayshan, A.M., Ahjel, S.W., Hashim, A.A. and Albeer, A.A.M.A. (2019). Molecular docking enabled updated screening of the matrix protein VP40 from Ebola virus with millions of compounds in the MCULE database for potential inhibitors. *Bioinformation*, 15(9): 627.

Posada, J. and Cooper, J.A. (1992). Molecular signal integration. Interplay between serine, threonine, and tyrosine phosphorylation. *Molecular biology of the cell*, 3(6): 583-592.

Su, J.Y., Erikson, E. and Maller, J.L. (1996). Cloning and characterization of a novel serine/threonine protein kinase expressed in early Xenopus embryos. *Journal of biological chemistry*, 271(24): 14430-14437.

Ten Dijke, P., Franzén, P., Yamashita, H., Ichijo, H., Heldin, C.H. and Miyazono, K. (1994). Serine/threonine kinase receptors. *Progress in growth factor research*, 5(1): 55-72.

Wang, Z., Bhattacharya, N., Weaver, M., Petersen, K., Meyer, M., Gapter, L. and Magnuson, N.S. (2001). Pim-1: a serine/threonine kinase with a role in cell survival, proliferation, differentiation and tumorigenesis. *Journal of veterinary science*, 2(3): 167-179.

Xiong, X., Tang, N., Lai, X., Zhang, J., Wen, W., Li, X., ... and Liu, Z. (2021). Insights into amentoflavone: a natural multifunctional biflavonoid. *Frontiers in pharmacology*, 12: 768708.

Yu, S., Yan, H., Zhang, L., Shan, M., Chen, P., Ding, A. and Li, S.F.Y. (2017). A review on the phytochemistry, pharmacology, and pharmacokinetics of amentoflavone, a naturally-occurring biflavonoid. *Molecules*, 22(2): 299.

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